REMARKS

Claims 1-41 are pending with claims 18, 19, 21, 22, 27, and 31-41 under examination. Applicants have amended claims 18, 21, 32, and 36 to indicate that Galectin-1 is administered "to the vicinity of the neural stem cells in the brain." The specification supports this amendment at, for example, page 10, lines 16-17. Applicants also amended claims 21 and 35 to correct a grammatical error. Applicants contend that these claim amendments do not add new matter.

Applicants acknowledge with appreciation the Office's withdrawal of the prior objections to the specification and to claims 21, 27, and 34. The Office maintains its rejection of claims 18, 19, 21, 22, 27, and 31-37 under 35 U.S.C. §103(a) and now newly rejects claims 38-41 under 35 U.S.C. §103(a). Applicants address these rejections below.

Horie in view of Wells

Claims 18, 19, 27, and 31-35 remain rejected under 35 U.S.C. §103(a) as allegedly obvious over U.S. Patent 6,890,531 ("Horie") in view of Wells et al. (*Cell* 64:91-97 (1991); "Wells"). According to the Office, Horie "teaches treatment of neuropathies of **central nerves** caused by nerve injuries . . . or degeneration of specific nerve system cells . . . wherein administration of galectin-1, contained in collagen, . . . is directly imbedded into the neurological location for treatment." Office Action, page 4; emphasis in original. Acknowledging that Horie is "silent as to cell proliferation induced by galectin-1 on neuronal stem cells on central nerve injury," the Office nonetheless concludes that "administration of galectin-1 to central nerves must have inherently induced neuronal stem cells proliferation, since Horie has performed the same step of

the claimed method, i.e., administration of galectin-1 to the brain." *Id.* The Office also notes that "anticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure." *Id.* at 5.

Regarding Wells, Applicants previously noted that this teaches that murine β-galactoside-binding protein (mGBP) is a *negative* regulator of cell proliferation, thus teaching away from a "method for enhancing *in vivo* proliferation." The Office now responds by citing to Wells for allegedly teaching that murine mGBP "is constitutively associated with cell growth and cell replication." *Id.* The Office attempts to dismiss Applicants' argument by explaining why Wells' method cannot be compared to the method taught in Horie:

> Wells results exhibiting inhibition of cell replication and cell arrest of embryonic fibroblasts involve extraction and purification of mGBP, different cell culture conditions and *in vitro* administration of mGBP at specific concentrations that were well above those required for effector molecules . . . . The steps in the method of Wells are not the same as the one claimed in the instant invention. The differences in the type of cultured cell use, source and dose of Galectin-1 used, and evaluation of results make any direct comparison of the data from the two studies (Horie and Wells) inappropriate. Indeed, post filing art of Vas et al., further corroborates how different concentrations of Galectin-1 result in opposing physiological regulation of cell growth and proliferation. Vas et al., teaches that *in vitro* administration of Galecin-1 is biphasic inducing proliferation and survival of murine and human hematopoietic stem at low concentrations whereas inhibiting cell growth and proliferation at high concentrations . . . . . Accordingly, the steps in the method taught by Wells and the method of the claimed invention differ to such extent that the resulting effects on cell growth and cell replication cannot be expected to be the same.

Office Action, pages 5 and 6. Applicants respectfully traverse.

If anything, the Office has explained why one of ordinary skill in the art would not have had a reasonable expectation of success in combining Horie with Wells. As the

Office admits, " [t]he differences in the type of cultured cell use, source and dose of Galectin-1 used, and evaluation of results make any direct comparison of the data from the two studies (Horie and Wells) inappropriate." And the Office appears to agree that Wells is not applicable to the claimed invention ("the steps in the method taught by Wells and the method of the claimed invention differ to such extent that the resulting effects on cell growth and cell replication cannot be expected to be the same"). The Office should not dismiss these significant differences and solely point to an alleged teaching in Wells that murine mGBP "is constitutively associated with cell growth and cell replication." Rather, the Office must consider the entirety of a reference's teaching. *See* MPEP § 2141.02 (VI). Based on the Office's own statements, one of ordinary skill in the art would not have combined the teachings of Horie with Wells to arrive at the claimed invention and even if the two references were combined, Wells teaches away from the claimed invention.

In addition, the Office may not use inherency as a basis of support for a rejection based on obviousness. Specifically, the Office alleges that "administration of galectin-1 to central nerves must have inherently induced neuronal stem cells proliferation, since Horie has performed the same step of the claimed method." As the MPEP instructs, however, "[o]bviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established." Section 2141.02 (V). Thus, whether or not this proliferation effect happens inherently as the Office suggests, this would not have rendered the claimed invention obvious.

Solely, to facilitate prosecution, however, Applicants have amended independent claims 18 and 32 to indicate that Galectin-1 is administered "to the vicinity of the neural stem cells in the brain." Contrary to the Office's alleged basis for inherency, Horie does

not teach administration of Galectin-1 to the vicinity of the neural stem cells in the brain and thus does not teach "the same step of the claimed method." The Office's cite to col. 13, lines 6-29 of Horie in no way suggests specifically delivering Galectin-1 to the vicinity of the neural stem cells.

For the reasons set forth above, Applicants contend that claims 18, 19, 27, and 31-35 would not have been obvious to one of ordinary skill in the art in light of Horie and Wells. Applicants therefore request that the Office withdraw this rejection.

Horie and Wells in view of Gage or Taupin

The Office continues to reject claims 21, 22, 36, and 37 under 35 U.S.C. §103(a) as allegedly obvious over Horie in view of Wells and in further view of U.S. Patent 6,436,389 ("Gage") or Taupin et al. (*Neuron* 28:385-97 (2000); "Taupin"). Applying Horie and Wells as discussed above, the Office relies on Gage for allegedly teaching "methods for treating neurodegenerative diseases . . . comprising stereotaxically inject[ing] into the rat hippocampus . . . neuronal progenitor cells . . . to stimulate neurogenesisin the adult rat subventricular zone." Office Action, page 7. The Office also alleges that Taupin similarly teaches "neuronal stem/progenitor cell division in the SVZ after stereotaxically injection into the rat hippocampus of genetically modified AHPs." *Id.* According to the Office, "Gage and Taupin complement the teachings of Horie and Wells in relation to the obviousness . . . to have induced proliferation of SVZ astrocytes by administration of Galectin-1 to the brain as this cell population displays neurogenic properties." *Id.* Applicants disagree.

The Office appears to cite both Gage and Taupin for allegedly teaching that the SVZ has "neurogenic properties." However, *arguendo*, even if this were true, this does not amount to specifically suggesting that Galectin-1, which is not discussed in either

Gage or Taupin, would facilitate proliferation of a SVZ astrocyte in particular. Moreover, as the Office has admitted, Horie and Wells cannot be compared to each other and therefore combined and even if they could be combined, Wells teaches away from "enhancing *in vivo* proliferation" using Galectin-1. Gage and Taupin contain no teachings that would rectify these shortcomings in Horie and Wells.

Solely, to facilitate prosecution, however, Applicants have amended independent claims 21 and 36 to indicate that Galectin-1 is administered "to the vicinity of the neural stem cells in the brain." For the reasons discussed above with regard to Horie and Wells, neither Horie, Wells, Gage, nor Taupin teach this method step either alone or in combination. Applicants therefore request that the Office withdraw this rejection.

Horie and Wells in view of Johansson

Claims 18, 21, 32, 36, and 38-41 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Horie in view of Wells and in further view of Johansson et al. (*Exper. Cell. Res.* 253:733-36 (1999); "Johansson"). Applying Horie and Wells as above, the Office notes that, regarding claims 38-41, these references do not "teach administration of Galectin-1 to the lateral ventricle of the brain." Office Action, page 10. The Office then relies on Johansson for allegedly teaching "two neurogenetic regions of the adult rodent brain: the wall of the lateral ventricle and the hippocampus." Johannson also allegedly teaches "self-renewing cells from the adult human lateral ventricle wall . . . capable of generating neurons, astrocytes, and oligodendrocytes *in vitro*. . . ." *Id.*

Based on the alleged teachings of Horie, Wells, and Johansson, the Office concludes that "it would have been *prima facie* obvious for one of skill in the art, as a matter of design of choice to administer Galectin-1 to any brain region associate[d] with

the contemplated treatment of a neurological disorders including the wall of the lateral ventricle and the hippocampus in order to ameliorate said neurodegenerative disorder in a subject, particularly because Johansson et al., discloses these two neurogenetic regions of the adult rodent brain suitable to develop therapies for neurodegenerative diseases." *Id.* at 11. In addition, the Office suggests that "there would have been a reasonable expectation of success . . . given the results of the [Horie, Well, and Johansson] demonstrating the success of the methodologies, and materials detailed in each of the disclosures." *Id.* Applicants disagree.

First, the Office contradicts itself in that on one hand it argues that the teachings and methods of Horie and Wells are very different and thus not comparable ("The differences in the type of cultured cell use, source and dose of Galectin-1 used, and evaluation of results make any direct comparison of the data from the two studies (Horie and Wells) inappropriate.") and now the Office argues that there would be a reasonable expectation of success based on an "inappropriate" comparison of the methods in Horie and Wells. The methodology discussed in Johansson describes the establishment of a tissue culture from dissociated hippocampus and lateral ventricle wall samples of two patients and does not involve the administration of Galectin-1 to the cells, let alone injection into the patient's brain. Thus, given that the methodology of Johannson is very different from the methodologies of Horie and Wells, the Office's own logic would dictate that it would be inappropriate to compare the methodology of Johansson to either Horie or Wells.

Moreover, the effects that growth factors or hormones can have on a cell are highly specific to the particular cell type because different types of cells express different sets of receptors. For example, EGF is specific to a certain small group of cell

types including epidermal cells while FGF is specific to another small group of cell types including fibroblasts. The cells which have the receptor only respond to the factor. However, even the same factor can exert different effects according to the type of the cells. When a certain factor works on a certain type of cells, one of ordinary skill in the art cannot predict that the factor can work on another type of cells. This cell-specific effect is known among persons of ordinary skill in the art (see, e.g., Molecular Biology of the Cell 5th ed. "Chapter 15. Mechanism of Cell Communication" Garland Publishing Inc.).

Horie identified Galectin-1 as a nerve regeneration-promoting factor (see col. 4, lines 37-46) and only performed sciatic nerve injury model experiment (see Example 18) and regeneration experiment of transected peripheral nerve (see Example 19). Neural stem cells are not known to be around the sciatic nerve used in Examples 18 and 19. There is no description, no suggestion, and no implication of proliferation of neural stem cells in Horie.

While the Office contends that Wells discloses that mGBP "is constitutively associated with cell growth and cell replication," the type of cell growth "regulation" in Wells is a negative regulation of cell proliferation, as Applicants explain above and in the prior-filed Amendment. For example, the second section of Wells' Results describes "Growth inhibition by mGBP". Wells, page 91. Wells also describes Galectin-1 as a negative regulator of cell growth at page 94, left column, lines 4-6 and page 95 left column, lines 4-6. Wells provides no suggestion or implication that Galectin-1 can enhance cell proliferation. Instead, this reference teaches away from the present invention, because it clearly demonstrated that Galectin-1 can arrest cell proliferation.

In addition, Wells uses fibroblasts and does not disclose neural stem cell explicitly nor implicitly. Considering that the action of growth factors is highly specific to the cell-type, one of ordinary skill in the art would not have been motivated to combine the teachings of Wells with Horie. Even if Wells suggested that Galectin-1 could stop proliferation of fibroblasts in the brain, which Applicants do not believe that Wells does, this is irrelevant to the claimed invention.

Even if Johansson teaches self-renewing cells from the adult human lateral ventricle wall and hippocampus, such a teaching in combination with Horie and Wells would not have rendered claims 38-41 obvious because Horie does not specifically disclose that Galectin-1 is involved in cell proliferation and Wells does not disclose neural stem cells.

Applicants discovered that Galectin-1 can enhance proliferation of neural stem cells. The combination of Horie, Wells, and Johannson in no way suggests specifically delivering Galectin-1 to the vicinity of the neural stem cells. This proliferation effect is unexpected and non-obvious from the cited references. Applicants therefore respectfully request that the Office withdraw this rejection.

Conclusions

Applicants respectfully requests that this Amendment under 37 C.F.R. § 1.116 be entered by the Office, placing claims 18, 19, 21, 22, 27, and 31-41 in condition for allowance. Applicants submit that the proposed amendments of claims 18, 21, 32, 35, and 36 do not raise new issues or necessitate the undertaking of any additional search of the art by the Office. Therefore, this Amendment should allow for immediate action by the Office.

Furthermore, Applicants respectfully point out that the final action by the Office presented some new arguments as to the application of the art against Applicant's invention. It is respectfully submitted that the entering of the Amendment would allow Applicants to reply to the final rejections and place the application in condition for allowance.

Finally, Applicants submit that the entry of the Amendment would place the application in better form for appeal, should the Office dispute the patentability of the pending claims.

In view of the foregoing remarks, Applicants contend that the claimed invention is not rendered obvious in view of the prior art references cited against this application. Applicants therefore request the entry of this Amendment, the Office's reconsideration and reexamination of the application, and the timely allowance of claims 18, 19, 21, 22, 27, and 31-41.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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